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Correlates of Syphilis Seroreactivity Among Pregnant Women: The HIVNET 024 Trial in Malawi, Tanzania, and Zambia

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Abstract

Objective—The objectives of this cross-sectional study were to determine correlates of syphilis seroprevalence among HIV-infected and -uninfected antenatal attendees in an African multisite clinical trial, and to improve strategies for maternal syphilis prevention.

Results—A total of 2270 (86%) women were HIV-infected and 366 (14%) were HIV-uninfected. One hundred seventy-five (6.6%) were syphilis-seropositive (7.3% among HIV-infected and 2.6% HIV-uninfected women). Statistically significant correlates included geographic site (odds ratio [OR]

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= 4.5, Blantyre; OR = 3.2, Lilongwe; OR = 9.0, Lusaka vs. Dar es Salaam referent); HIV infection (OR = 3.3); age 20 to 24 years (OR = 2.5); being divorced, widowed, or separated (OR = 2.9); genital ulcer treatment in the last year (OR = 2.9); history of stillbirth (OR = 2.8, one stillbirth; OR = 4.3, 2–5 stillbirths); and history of preterm delivery (OR = 2.7, one preterm delivery).

Conclusion—Many women without identified risk factors were syphilis-seropositive. Younger HIV-infected women were at highest risk. Universal integrated antenatal HIV and syphilis screening and treatment is essential in sub-Saharan African settings.

Syphilis is a serious cause of maternal and infant morbidity and mortality.^{1–5} Syphilis during pregnancy is associated with stillbirth, spontaneous abortion, preterm birth, and intrauterine growth restriction.⁶ A *Treponema pallidum*-infected newborn may exhibit hepatosplenomegaly, failure to thrive, and high neonatal mortality.^{5,7–9} In addition to these serious reproductive outcomes, syphilis is a well-documented cofactor for horizontal (sexual),^{10–12} as well as vertical (mother to child), transmission of HIV.^{10,13,14} In sub-Saharan Africa and elsewhere, syphilis and HIV serve as synergistic infections, each exacerbating the transmission of the other.^{15,16}

Women in resource-limited settings may not receive routine screening for syphilis in antenatal care, and even if they are screened, treatment for infected mothers may be unavailable.⁷ In a chart review of 622 women receiving public sector antenatal care in Lusaka, Zambia, the rapid plasma reagin (RPR) assay was recorded in 81% of records, whereas only 2 of 44 positive results had treatment documented in their records at a time of penicillin supply shortages (1999–2000) (R. MacDonald and SHV, unpublished data; M. Sinkala, personal communication, May 2005).

Reported syphilis rates vary markedly between and within sub-Saharan African populations. Antenatal syphilis prevalence rates in Malawi, Tanzania, and Zambia are reported as 2.7% (year 2003; Venereal Diseases Reference Laboratory tests [VDRL], no confirmatory testing),¹⁷ 7.2% (year 2000; RPR confirmed with *T. pallidum* hemagglutination assay [TPHA]),¹⁸ and 8.2% (2001; RPR confirmed with TPHA),¹⁹ respectively. Regional seroprevalence differences may reflect a variety of sociocultural and economic factors, varying surveillance methods, and differential access to syphilis diagnosis and treatment.²⁰ We examined demographic, sexual risk, and obstetric characteristics to predict syphilis sero-prevalence among HIV-infected and -uninfected antenatal attendees enrolled in a multisite clinical trial in Africa.

Methods

Study Setting and Population

The HIVNET 024 trial was a randomized, double-blind, placebo-controlled phase 3 clinical trial of antibiotics to prevent perinatal HIV transmission and preterm birth by reducing chorioamnionitis.^{21,22} The intervention studied in the trial was a relatively inexpensive (<\$5 US), 2-course antibiotic prophylactic regimen. Trial participants were recruited in 4 sub-Saharan African cities: Blantyre and Lilongwe, Malawi; Lusaka, Zambia; and Dar es Salaam, Tanzania. Enrollment started in July 2001 and was completed in February 2003. Consenting pregnant women were screened for HIV infection between 16 and 23 weeks gestation during an antenatal clinic visit before enrollment into the trial. Laboratory evaluations included HIV-1 serology screening by dual rapid test algorithm and Western blot confirmation of all positive or indeterminate results at 3 sites, whereas the Dar es Salaam site performed 2 enzyme-linked immunosorbent assays (ELISAs): Dade Behring Enzygnost anti-HIV-1/2 Plus (first ELISA) followed by Abbott Murex Wellcozyme anti-HIV-1 recombinant with discrepant results between the two ELISAs being confirmed by Western blot. Additional study laboratory evaluations included comprehensive screening for sexually transmitted infections (STIs) and

complete blood counts.²¹ At 20 to 24 weeks gestational age, women were randomized to receive either 250 mg metronidazole 3 times a day and 250 mg erythromycin orally 3 times daily for 7 days or placebo for the control group. Participants were also given 250 mg metronidazole and 500 mg ampicillin (or placebo) at the 26- to 30-week visit to be taken at the onset of labor continuing after delivery 3 times daily until the 1-week course was completed. Five HIV-infected women were recruited for every one HIV-uninfected woman at the 2 Malawi and Zambian sites, whereas the Dar es Salaam site recruited only HIV-infected women as per the design of the parent trial. The primary study outcome was mother-to-child transmission of HIV, whereas secondary outcomes included other causes of morbidity and mortality such as preterm birth. Sociodemographic, living environment, obstetric, and sexual history data were collected at the study enrollment visit using a standardized structured questionnaire enabling the present nested study. Research nurses interviewed enrolled participants confidentially in private rooms. The study was approved by U.S. and in-country institutional ethical review boards or committees in each country. Written informed consent was obtained from all enrolled participants.

Laboratory Procedures

HIV testing was performed at a screening visit according to site-specific procedures using either conventional HIV ELISA tests or dual HIV rapid tests. These tests were validated by a central reference laboratory in the United States. HIV-infected women were offered mother-to-child transmission prophylaxis with nevirapine.^{23,24} Women were tested for syphilis using RPR tests (Blantyre, Lilongwe, and Lusaka) or VDRL tests (Dar es Salaam) as part of preentry evaluations at the enrollment visit. Confirmation of the syphilis screening test was performed with the microhemagglutination *T. pallidum* test (MHA-TP) (Lilongwe), *T. pallidum* particle agglutination test (TPPA) (Dar es Salaam), or TPHA (Blantyre). Both TPPA and TPHA tests were used to confirm positive RPR samples from Lusaka. Women with a reactive syphilis test were treated with intramuscular benzathine penicillin at no cost.

Statistical Analysis

For purposes of this study, a confirmed test was used as the basis for syphilis diagnosis. Data obtained at the enrollment visit (20–24 weeks gestation) were used for this study. A woman was considered to have maternal syphilis if, at the time of HIVNET 024 enrollment, her serum was reactive according to one of the screening and one of the confirmatory tests. Higher socioeconomic status was estimated from data on availability of electricity or running water in the home.

Associations between syphilis serostatus and demographic, sexual history, or obstetric variables were assessed using odds ratios (ORs) and chi-square, Student t, or Fisher exact tests, as appropriate, to determine statistical significance. Multivariable logistic regression analysis was used to further investigate those associations that were significant at a $P < 0.05$ (2-tailed) level with syphilis sero-prevalence in the bivariate analyses. Findings are presented as adjusted odds ratios (OR_{adj}) with corresponding 95% confidence intervals (95% CIs) and/or P values. The logistic models were performed for the overall population of HIV-infected and -uninfected women and separately stratified by HIV infection status. All statistical analyses were performed with SAS version 9.1 (SAS, Inc., Cary, NC).

Results

Study Population, Syphilis Seroprevalence

Of 2661 women who gave informed consent for enrollment into HIVNET 024, 2636 (99%) had a syphilis screening test and, if the screening test was positive, a confirmatory test. All 2636 of these women were included in this syphilis substudy. As per the study design, 2270

(86%) were HIV-infected and 366 (14%) were HIV-uninfected. At enrollment, 175 (6.6%) women were confirmed syphilis positive, 7.3% among HIV-infected and 2.5% among HIV-uninfected (OR = 3.1, 95% CI = 1.6–6.2). Overall site-specific seroprevalence rates ranged from 1.4% in Dar es Salaam, Tanzania, to 11.7% in Lusaka, Zambia. The rates were intermediate in Lilongwe (5.1%) and Blantyre (6.3%), Malawi (Table 1). Among the HIV-infected women, the site-specific syphilis seroprevalences were: 1.4% in Dar es Salaam, 5.9% in Lilongwe, 7.3% in Blantyre, and 13.0% in Lusaka. Among the HIV-uninfected women, the site-specific confirmed syphilis rates were: 1.1% in Blantyre, 1.4% in Lilongwe, and 4.9% in Lusaka.

Sociodemographic Characteristics, Sexual and Obstetric History

In bivariate analyses, women were more likely to be syphilis-seropositive if they came from the Malawi or Zambia sites, were HIV-infected, were 20 to 24 years old, had completed less than 6 years of formal education, were illiterate, were divorced/separated/widowed, were of lower socioeconomic status, had a greater number of lifetime sexual partners, had been treated for genital ulcers in the last year, had a greater number of past pregnancies, had a history of stillbirth, and a history of preterm delivery (Table 1).

In bivariate analyses, the following variables were not significant: years of formal education of spouse/partner, occupation, spouse/partner's occupation, housing type, use of gas/electrical or charcoal stove or firewood for cooking, number of lifetime sexual partners in the current pregnancy, condom use during the current pregnancy, having been treated for abnormal vaginal discharge in the last year, and number of abortions or miscarriages.

Women at each of the 4 sites were of similar age, education, literacy, marital status, and occupation, except that women in Dar es Salaam were of higher socioeconomic status as measured by electricity and running water on their premises and use of a paraffin stove or firewood for cooking. Results of site-specific analyses were very similar to the findings of the overall analysis (data not shown).

Correlates of Syphilis Seroprevalence

In the multivariable logistic regression analysis for the 4 sites combined, 7 factors were found to be independent and statistically significant correlates of syphilis seroprevalence among the antenatal attendees (Table 2): geographic site (OR = 4.5, Blantyre; OR = 3.2, Lilongwe; OR = 9.0, Lusaka, vs. Dar es Salaam referent population), HIV infection (OR = 3.3), maternal age 20 to 24 years (OR = 2.5 vs. age 16–19 years), being divorced/widowed/ separated (OR = 2.9 vs. married or living with partner), having had treatment for genital ulcers in the last year (OR = 2.9), history of stillbirth (OR = 2.8 for one stillbirth; OR = 4.3 for 2–5 stillbirths), or having had a preterm delivery (OR = 2.7 for one preterm delivery).

The same variables were found significant in bivariate analyses for the HIV-infected women as for the combined cohort and were used in a multivariable analysis assessment. The multivariable logistic regression analysis results were similar for the combined HIV-infected and -uninfected cohort (n = 2636) as for the HIV-infected cohort alone (n = 2270) (results not shown for HIV-infected cohort). There were 9 syphilis-seropositive women among the HIV-uninfected cohort of women (n = 366). No variables were found to be independent and statistically significant correlates of syphilis seroreactivity among the HIV-uninfected women in multivariable analysis.

Discussion

There were variations in syphilis seroprevalence among sites, with the Lusaka, Zambia, site having an especially high seroprevalence (11.7%). Women with HIV infection were more likely to be syphilis-seropositive as were women who were divorced, separated, or widowed. Women with a history of stillbirth or preterm delivery were significantly more likely to be syphilis-seropositive, confirming the well-known reproductive health consequences of maternal and congenital syphilis. A surprising result was the significant association of syphilis among women in the 20- to 24-year age group as compared with older women. Typically, syphilis rates are highest in older women, but given 86% of women enrolled in the study were HIV-infected and the extremely limited access to antiretroviral therapy in the time period of the study, older women with syphilis and HIV may well have died before study commencement, distorting the age-risk associations.²⁵ Although the number of sexual partners during the current pregnancy was not significantly associated with syphilis, the number of lifetime sexual partners was found to be statistically significant on bivariate and multivariable analyses, suggesting that syphilis risk is not specific to the time of pregnancy per se.^{10,26}

Higher syphilis risk is documented in divorced and widowed women in Senegal,²⁷ although single marital status was the risk factor noted in a previous Tanzania study.²⁸ Previous studies related to pregnant women in developing countries reported the following risk factors for maternal syphilis, similar to our findings: HIV infection,²⁹ history of stillbirth,³⁰ history of preterm delivery,³¹ previous perinatal death,³² high-risk sexual behaviors,³³ history of abortion,³⁴ genital ulcer disease,³⁵ and lower socioeconomic status.³⁶ The economic indicators in this study (presence of water or electricity in the home) suggest that antenatal attendees in Dar es Salaam had a higher socioeconomic status, perhaps associated with lower sexual and syphilis risks. Higher socioeconomic status is associated with decreased syphilis seroreactivity.^{33,37,38} A history of stillbirth was significantly associated with syphilis seroreactivity in our study; in southern Africa, up to half of all stillbirths are found in syphilis-seroreactive women, with $\leq 25\%$ of all stillbirths being attributed to syphilis.³⁹

In a study of 1058 HIV-infected women in Dar es Salaam, Tanzania (2001), antenatal attendees, independent risk factors for syphilis seroreactivity (positive on both VDRL and TPHA) were: age 20 to 24 years and 30 to 34 years (compared with women 15–19 years old), abnormal vaginal discharge in the past year, a genital ulcer on examination, or current *Trichomonas vaginalis* infection.⁴⁰ Women who were fully supported by their male partners were at a reduced risk of active syphilis compared with those with their own personal income source.⁴⁰

Inefficient and ineffective antenatal syphilis screening programs in developing countries are well documented.^{7,41–44} Although each of the women enrolled in this study was screened for syphilis and, if reactive, treated, we do not know the coverage rates of the antenatal syphilis screening programs in these 4 sites for nonresearch patients. In Zambia and Malawi, in particular, high seroprevalence rates suggest the need to improve syphilis screening and treatment in concert with other essential antenatal services.⁴⁵ Advocacy by developing country governments and international economic and/or technical assistance is needed to support strapped health workers and systems to achieve a long-term goal of sustainability.

Our seroprevalence findings are a legitimate comparison between 4 African cities, but they might not reflect background syphilis seroprevalence because: 1) 86% of the women were HIV-infected as a result of the design of the parent clinical trial; 2) antenatal attendees who consented to join the research study may have been more likely to have had STIs or history of obstetric complication than other women; and 3) recruitment for the study occurred among women already in the antenatal care system; thus, women who joined the study were those who “booked early” because enrollment only occurred from 20 to 24 weeks gestation. These

selection factors indicate that our study seroprevalence is not generalizable; higher syphilis seroprevalence might be expected from HIV-infected women; lower rates might be seen in women booking relatively early (20–24 weeks gestation) for antenatal care; higher rates might be seen in women booking early as a result of reproductive tract symptoms; and lower rates might be seen in women seeking care through research-related programs because they potentially perceived it of higher quality than the government care system. We did not find the higher syphilis rates among HIV-infected women in the lower HIV prevalence nation; the lowest syphilis rates were noted in Tanzania where HIV prevalence is lower than in Malawi or Zambia.^{46,47}

Antenatal syphilis screening programs must be evaluated for effectiveness and reformed accordingly. Infants receiving antiretroviral prophylaxis as part of a prevention of mother-to-child HIV transmission (PMTCT) program have been documented to die of congenital syphilis in a program in which syphilis screening had not been a part of HIV prevention activities.⁴⁸ Vertical integration of syphilis screening in antenatal HIV prevention programs is a way to strengthen existing health systems and to improve on health outcomes, particularly in resource-limited settings where obstacles to universal antenatal screening may abound⁴⁸ analogous to joint HIV and tuberculosis screening that is advocated in high-prevalence regions.⁴⁹ A routine, universal, “opt-out” approach to joint syphilis and HIV screening would improve coverage and care for both.⁵⁰ In Lilongwe, Malawi, for example, where a mature PMTCT program has resulted in almost universal acceptance of voluntary counseling and testing (VCT) based on fingerstick, whole-blood HIV rapid testing, a pilot program is being conducted to routinely perform syphilis rapid tests (and treatment) during the VCT session.⁵¹ Given the high rates of HIV and syphilis coinfection, antenatal care providers may consider an antenatal attendee’s marital status and age; if resources are scarce and must be prioritized, those attendees who are younger, divorced, widowed, or separated are likely to be at higher risk for both infectious diseases. Although recognition of syphilis risk factors is useful, many women without the risk factor characteristics were syphilis-seroreactive; universal testing is clearly the superior approach.

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TABLE 1

Confirmed Syphilis-Seropositive and Baseline Sociodemographic and Sexual/Obstetric History Characteristics Among 2636 Enrolled Antenatal Attendees in the HIVNET 024 Clinical Trial in Sub-Saharan Africa

Characteristic	Women n (%)	Percent Confirmed Syphilis-Seropositive and <i>P</i> Value
Site	n = 2,636	
Blantyre, Malawi	559 (21.2)	6.3
Lilongwe, Malawi	896 (34.0)	5.1
Dar es Salaam, Tanzania	428 (16.2)	1.4
Lusaka, Zambia	753 (28.6)	11.7
		<i>P</i> <0.0001
HIV serostatus	n = 2,636	
Positive	2,270 (86.1)	7.3
Negative	366 (13.9)	2.5
		<i>P</i> = 0.0005
Age in years	n = 2,636	
16–19	322 (12.2)	3.7
20–24	1,013 (38.4)	9.1
25–29	845 (32.1)	5.3
30–45	456 (17.3)	5.7
		<i>P</i> = 0.0007
Years of formal education (completed years)	n = 2,635	
None	233 (8.8)	10.3
1–5	614 (23.3)	8.5
6–18	1,788 (67.9)	5.5
		<i>P</i> = 0.002
Literate (self-reported)	n = 2,636	
Yes	2,051 (77.8)	5.3
No	585 (22.2)	11.3
		<i>P</i> ≤0.0001
Marital status	n = 2,636	
Married and/or living with partner (referent)	2,431 (92.2)	6.3
Never married or living with partner	141 (5.4)	4.3
Divorced, separated, or widowed	64 (2.4)	23.4
		<i>P</i> ≤0.0001
Electricity on premises	n = 2,636	
Yes	1,048 (39.8)	5.1
No	1,588 (60.2)	7.7
		<i>P</i> = 0.008
Running water on premises	n = 2,636	
Yes	1,084 (41.1)	5.3

Characteristic	Women n (%)	Percent Confirmed Syphilis-Seropositive and P Value
No	1,552 (58.9)	7.6
		$P = 0.02$
Cook with paraffin stove	n = 2,636	
Yes	470 (17.8)	2.3
No	2,166 (82.2)	7.6
		$P \leq 0.0001$
Number of lifetime sexual partners including spouse or partner	n = 2,617	
1	628 (24.0)	4.6
2	848 (32.4)	5.7
3–25	1,141 (43.6)	8.5
		$P < 0.003$
In the last year, treated for genital ulcers	n = 2,633	
Yes	93 (3.5)	21.5
No	2,540 (96.5)	6.1
		$P \leq 0.0001$
Number of pregnancies, including current	n = 2,636	
1	501 (19.0)	4
2–4	1,712 (65.0)	7.3
5–12	423 (16.1)	7.1
		$P = 0.03$
Number of stillbirths	n = 2,636	
0	2,425 (92)	5.7
1	180 (6.8)	15.6
2–5	31 (1.2)	25.8
		$P \leq 0.0001$
Number of children born >3 wk early	n = 2,636	
0	2,509 (95.2)	6.2
1	95 (3.6)	16.8
2–8	32 (1.2)	9.4
		$P = 0.002$

TABLE 2

Results of Multivariable Analysis: Risk Factors for Syphilis (RPR or VDRL + with confirmation by TPHA, MHA-TP, or TPPA)

Characteristic	Crude Adjusted		
	Odds Ratio	Odds Ratio (95% confidence interval)	P Value
Site			
Dar es Salaam, Tanzania (referent)	1.0	1.0	
Blantyre, Malawi	4.7	4.5 (1.4–14.4)	0.01
Lilongwe, Malawi	3.8	3.2 (1.0–10.0)	0.04
Lusaka, Zambia	9.3	9.0 (2.9–28.2)	0.0002
HIV infection status			
Seronegative (referent)	1.0	1.0	
Seropositive	3.1	3.3 (1.6–6.9)	0.002
Age (years)			
16–19 (referent)	1.0	1.0	
20–24	2.6	2.5 (1.3–5.0)	0.01
25–29	1.5	1.2 (0.6–2.6)	0.6
30–45	1.6	1.4 (0.6–3.2)	0.4
Formal education (completed years)			
0 (referent)	1.0	1.0	
1–5	0.8	0.9 (0.5–1.5)	0.6
6–18	0.5	0.7 (0.4–1.5)	0.4
Literacy (self-reported)			
Not able to read (referent)	1.0	1.0	
Able to read	0.4	0.7 (0.4–1.2)	0.2
Marital status			
Married/living with partner (referent)	1.0	1.0	
Never married/not living with partner	0.7	0.8 (0.3–2.0)	0.7
Divorced/separated/widowed	4.5	2.9 (1.5–5.7)	0.001
Presence of utilities on premises			
No electricity (referent)	1.0	1.0	
Electricity on premises	0.6	0.9 (0.6–1.3)	0.5
No running water on premises (referent)	1.0	1.0	
Running water on premises	0.7	0.9 (0.6–1.3)	0.6
Method used for daily cooking			
No paraffin stove (referent)	1.0	1.0	
Paraffin stove	0.3	1.1 (0.5–2.6)	0.8
Number of lifetime sexual partners including spouse			
1 (referent)	1.0	1.0	
2	1.2	1.1 (0.7–1.9)	0.6
3–25	1.9	1.5 (1.0–2.4)	0.1
In the last year			

Characteristic	Crude Adjusted		P Value
	Odds Ratio	Odds Ratio (95% confidence interval)	
Not treated for genital ulcers (referent)	1.0	1.0	
Treated for genital ulcers	4.2	2.9 (1.6–5.3)	0.0003
Number of pregnancies, including this pregnancy			
1 (referent)	1.0	1.0	
2–4	1.9	1.5 (0.8–2.5)	0.2
5–12	1.8	1.2 (0.6–2.7)	0.6
Number of stillbirths			
0 (referent)	1.0	1.0	
1	3.0	2.8 (1.7–4.5)	<0.0001
2–5	5.7	4.3 (1.7–11.2)	0.002
Number of children born >3 wk early			
0 (referent)	1.0	1.0	
1	3.1	2.7 (1.5–5.0)	0.002
2–8	1.6	1.5 (0.4–5.4)	0.5

RPR indicates rapid plasma reagin assay; VDRL = venereal diseases reference laboratory tests; TPHA = *treponema pallidum* hemagglutination assay; MHA-TP = microhemagglutination *T. pallidum* test; TPPA = *T. pallidum* particle agglutination test.